Exhibit 1

United States District Court
for the Western District of Oklahoma

Richard Glossip, *et al.*,
Plaintiffs,
v.
Randy Chandler, *et al.*,
Defendants.

No: 14-cv-665-F

EXPERT REPORT OF JOSEPH F. ANTOGNINI, M.D., M.B.A.

JOSEPH F. ANTOGNINI, does hereby declare and say:

1. My name is Joseph F. Antognini. I am a medical doctor, board-certified in anesthesiology. I received a B.A. degree from the University of California, Berkeley in Economics in 1980. I received my M.D. degree from the University of Southern California in 1984. I also received an M.B.A. from California State University, Sacramento in 2010. I was previously the Director of Peri-operative Services at the University of California, Davis Health System and a Professor of Anesthesiology and Pain Medicine and Professor of Neurobiology, Physiology and Behavior at the University of California, Davis. I am licensed to practice medicine in the State of California. I have over 30 years of experience practicing anesthesiology since 1984 when I began my residency at the University of California, Davis Health System. I am the author or co-author of over 200 publications. My area of research has focused on anesthetic mechanisms, specifically related to where anesthetics produce unconsciousness, amnesia and immobility. A true and correct copy of my curriculum vitae is attached hereto as Exhibit A.

Scope of Engagement

2. I have been asked to render expert opinions in the fields of general medicine and

anesthesiology, especially regarding the use, actions and efficacy of midazolam, in relation to the Oklahoma's lethal injection protocol, and the effectiveness of the procedures therein. This report contains a complete statement of my opinions, and the basis and reasons therefor, including the facts or data I have considered in forming them. I may supplement this report as appropriate. The opinions that I do provide are within my field of anesthesiology and such fields as are necessarily related to anesthesiology, including general medicine, pharmacology and physiology, and fall within the scope of my expertise. All opinions expressed herein are stated to a reasonable degree of medical and scientific certainty unless otherwise noted.

Materials Reviewed

3. I have reviewed, and am familiar with, the allegations made in the Third Amended Complaint, *Richard Glossip et al., vs. Randy Chandler, et al.* (dated 7-6-2020), Oklahoma's execution protocol (dated 2-20-2020), publications in the "References Cited" section and additional information in the documents described below. I am familiar with the issues related to executions in other litigation as listed in Paragraph 5 below.

4. Should additional documents or information be provided to me for review and analysis, I may take those additional materials into account, and modify and/or supplement my opinions accordingly. If I am present at hearings and/or trial in this case, I may take into account any testimony or other evidence to the extent related to my opinions and modify and/or supplement my opinions accordingly. In performing my analysis, I have relied on my professional training, education and experience. The opinions presented in this report are my opinions and mine alone. I have reviewed and considered documents and information and identified those materials above. These documents and other information that I reviewed and considered are of a type reasonably relied upon by experts in the field of anesthesiology, general medicine, physiology and

pharmacology in forming opinions or inferences on questions in this area. I have looked upon all of these as valuable sources of information that I am obliged to consider.

5. I have testified and submitted expert reports in the following cases in the past four years: 1) I have submitted a report in *Richard Jordan, et al., v. Marshall L. Fisher, et al.,* (U.S. District Court, Southern District of Mississippi, Northern Division, Civil Action No. 3:15-cv-00295) a case related to the use of midazolam for lethal injection; 2) I have submitted reports and have been deposed in *Russell Bucklew v. George A. Lombardi, et al.,* (U.S. District Court, Western District of Missouri, Case No. 4:14-CV-8000-BP) a case related to the use of pentobarbital for lethal injection (later *Bucklew v. Precythe*, US Supreme Court case No. 17-8151); 3) I have submitted reports and testified in *In re: Ohio Execution Protocol Litigation; Phillips, Tibbets & Otte, Henness, Jackson, et al., Plaintiffs,* (U.S. District Court, Southern Division of Ohio, Case No. 2:11-cv-1016), cases related to the use of midazolam for lethal injection; 4) I have submitted reports and testified in *McGeehee v. Hutchison,* No. 4:17-cv-00179-KGB, and *Williams v. Kelly*, No. 5:17-cv-00103-JM, No. 5:17-00179-KGB, related to the use of midazolam for lethal injection in Arkansas (testimony April 2017 and April 2019; U.S. District Court, Eastern District Arkansas); 5) I submitted a report in *Rhines v. South Dakota Department of Corrections, et al*., 49CIV19-002940, 2nd Judicial Circuit, County of Minnehaha, State of South Dakota, dated 10-26-2019; 6) I have submitted reports and given testimony *In the Matter of the Federal Bureau of Prisons' Execution Protocol Cases* (No. 19-mc-00145-TSC).

6. **SUMMARY OF OPINIONS HEREIN STATED**:

a. Midazolam can be used, and has been used, as the sole medication to induce anesthesia in a variety of otherwise painful medical procedures, including laryngoscopy, followed by endotracheal intubation, a procedure

which is very stimulating;

b. Midazolam produces unconsciousness and by itself can be fatal;

c. Paralysis and lack of breathing following administration of a drug such as vecuronium or rocuronium would not be perceived by a person rendered unconscious by 500 mg midazolam;

d. Intravenous infusion of potassium chloride would not be perceived as painful in a person rendered unconscious by 500 mg midazolam;

e. The Oklahoma lethal injection protocol provides for sufficient time for midazolam to produce unconsciousness before administration of a paralytic drug and potassium chloride;

f. Any pulmonary edema that might occur ante mortem is not likely to be experienced by a person who has been administered 500 mg midazolam;

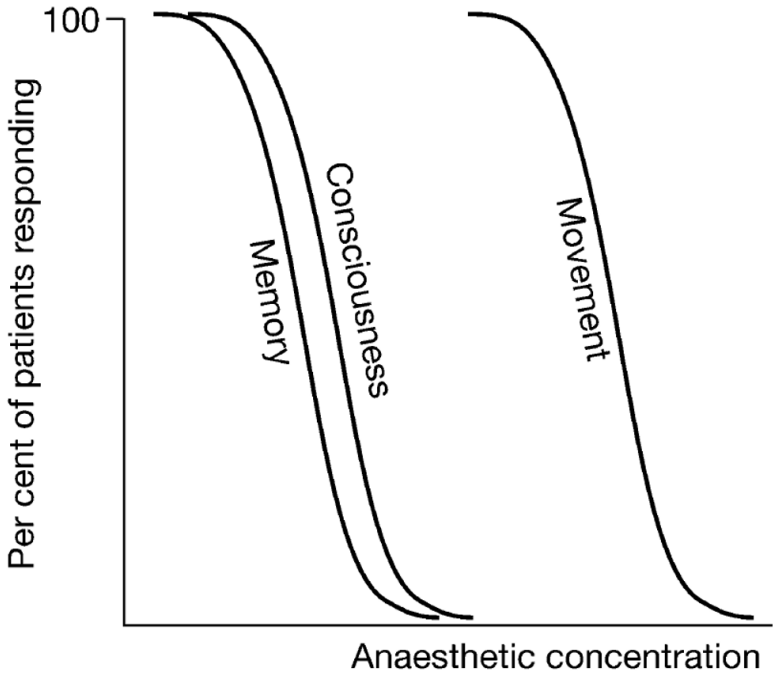
g. The Oklahoma protocol specifies that members of the execution team, including the IV team members, will possess the requisite training and experience to place intravenous lines, adequately determine unconsciousness using medically appropriate methods, and to determine whether the condemned inmate has been rendered sufficiently unconscious so as to be unaware of any pain produced by administration of the paralytic drug and the potassium chloride;

h. Alternate methods of execution, such as the firing squad, will result in pain and suffering.

Relationship between level of anesthesia, unconsciousness, immobility and noxious stimuli

7. Essential end-points of general anesthesia include amnesia, unconsciousness and immobility in response to a noxious stimulus (Antognini and Carstens, 2002; Perouansky et al., 2019). Amnesia is needed because patients do not want to remember their surgery. Unconsciousness is needed because patients do not want to be awake, conscious and aware of procedures that would otherwise be painful (and surgery personnel also would not want that for their patients). Immobility is needed because surgeons do not want to perform surgery on a moving target. Indeed, the success of the first public demonstration of general anesthesia was due, in large part, to the immobility (in response to surgical incision) the anesthetic produced. These distinctions of the end-points are important because people (both healthcare personnel and laypeople) equate movement during surgery to consciousness. In fact, patients often move during surgery, but they are rarely conscious or awake. The doses (or effect-site concentrations) needed to produce amnesia and unconsciousness are generally 25-50% of the doses needed to produce immobility (Antognini and Carstens, 2002; Perouansky et al., 2019). This concept is demonstrated in the figure below indicating that as the anesthetic concentration (or dose) is increased the percent of patients who retain memory and consciousness decreases to zero, but these same patients will move involuntarily to noxious stimulation (figure adapted from

Antognini and Carstens, 2002, and reproduced in Perouansky et al., 2019).



8. The relationship above holds true for intravenous drugs. For example, Smith et al. (1994) found that the propofol concentration required to produce unconsciousness (response to verbal command) was approximately 25% of that needed to produce immobility to a skin incision. Because midazolam has never been studied in humans at doses that could produce immobility, the exact relationship between midazolam concentrations that produce unconsciousness and immobility is not known. Glass et al. (1997), however, determined that the midazolam plasma concentration to produce unconsciousness in 50% of individuals was 270 ng/ml. Inagaki et al. (1993) reported that midazolam in plasma at 539 ng/ml reduced halothane requirements for immobility by 70%. If midazolam reduced halothane in a strict linear manner beyond the 539 ng/ml point, a midazolam concentration of about 770 ng/ml would produce immobility. As a conservative estimate, then, the concentration of midazolam producing unconsciousness is about 35% of that predicted to cause immobility. However, because higher concentrations of

midazolam are likely required to produce immobility, that percentage would be smaller, but still comparable to other anesthetics. But the important point is that the dose of midazolam needed to produce unconsciousness is far below that needed to produce immobility.

9. There is overwhelming evidence that anesthetics produce immobility (in response to noxious stimulation) by an action in the spinal cord (Antognini and Schwartz, 1993; Rampil et al., 1993), and that movement that occurs during noxious stimulation in an otherwise anesthetized subject is a spinal cord-mediated process, independent of the brain. In fact, brain dead humans have demonstrated complex movements, including crossing of the arms over the chest, sitting up in bed, and turning of the head; this phenomenon is called the Lazarus sign (Heytens et al., 1989; Jain and DeGeorgia, 2005; Wu and Balaguer, 2013). Thus, the spinal cord is capable of producing complex movements, and patient movements during surgery do not necessarily indicate consciousness.

10. It is important to distinguish between pain and a noxious stimulus. Pain is the conscious awareness of an actual (or perceived) noxious stimulus. Similarly, as defined by the International Association for the Study of Pain, pain is "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." The IASP defines a noxious stimulus as "A stimulus that is damaging or threatens damage to normal tissues." (see IASP website[1]). Taken together, these two definitions lead to the conclusion that a noxious stimulus is normally assumed to be "painful" when it is applied to a conscious subject. However, movement that occurs during noxious stimulation during anesthesia does not necessarily equate to a person being conscious and experiencing pain.

1 https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698 accessed 1-15-2021

11. Because anesthetics produce unconsciousness, anesthetized patients cannot perceive pain. And, because midazolam can produce sufficiently deep unconsciousness, a person administered midazolam in large, supra-clinical doses (i.e., beyond the normal clinical and therapeutic range) cannot perceive pain, as further explained below.

12. Many studies (perhaps hundreds or thousands) in animals and humans have used the concept of "minimum alveolar concentration" (MAC) as the standard of anesthetic potency (original study: Eger et al., 1965). It is, essentially, an effective drug dose that would produce immobility in response to noxious stimulation in 50% of subjects. In a typical human MAC study, the patient is anesthetized with the anesthetic being studied and the anesthetic dose or concentration is adjusted and a supra-maximal noxious stimulus is then applied (a surgical incision, or electrical stimulus for 30-60 sec, for example). The subject is then observed for "gross, purposeful movement" which is usually defined as movement of another extremity or turning of the head towards the stimulus; a simple withdrawal reflex, coughing, chewing or straining are defined as "no movement" for these purposes. The term "supra-maximal" indicates that a stronger stimulus would not require more anesthesia. Thus, during surgical procedures, there can be a spectrum of movements, including slight stiffening of various muscles, coughing, arm movement and vigorous thrashing about, yet, these patients are rarely aware and rarely have explicit memory of these events. Summarizing #7-12 above, an individual who has received sufficient doses of sedatives/anesthetic drugs, and who moves as the result of a noxious stimulus, is not necessarily aware, notwithstanding the movement.

Actions of Midazolam

13. Midazolam is a short-acting benzodiazepine which is commonly used as a sedative in routine medical procedures such as colonoscopies, bronchoscopies, and other minor medical

procedures, as well as prior to surgery. Immediately prior to a procedure, a typical therapeutic dose of midazolam is 2 – 3 mg for a 70 kg (150-155 pounds) adult less than 65 years old, although more might be used during a procedure; lesser doses are required in patients over 65 years old because of the increased sensitivity in these patients (Rivera & Antognini, 2009). A total dose greater than 5 mg is not usually necessary to reach the usual desired endpoint of moderate sedation; doses above 5 mg must be used with extreme caution because of the well-known risks of unconsciousness, respiratory depression, apnea (lack of breathing) and death (see package insert).[2] When a therapeutic dose of midazolam is administered intravenously, the onset of action is rapid, with peak effects within 2-3 minutes (Vuyk et al., 2019). The therapeutic dose serves two primary purposes. First, it relieves the patient's anxiety and serves as a powerful sedative. Second, the drug causes amnesia, and thus prevents memory formation, especially of unpleasant and painful events (Vuyk et al., 2019).

14. Midazolam can result in unconsciousness, coma, respiratory arrest, and death, even at therapeutic doses, but especially at greater doses. The inherent danger of midazolam was rapidly noticed after its introduction and a "Black Box Warning" was issued just three years after the introduction of midazolam into clinical practice (Lasser et al, 2002). A "Black Box Warning" signifies that a drug is particularly dangerous and is associated with serious side effects; in the case of midazolam, these side effects are respiratory depression, unconsciousness and death. Finally, the package insert clearly states that midazolam is indicated "…..for induction of general anesthesia…".

2 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208878Orig1s000lbl.pdf accessed 1-15-2021

15. Midazolam depresses respiration and causes apnea (lack of breathing). In a chapter in Miller's Anesthesia (Vuyk et al., 2019), the following statement is written: "Benzodiazepines, similar to most IV anesthetics, produce dose-related central respiratory system depression".

16. When midazolam first entered clinical practice, numerous adverse outcomes were reported to the United States Department of Health and Human Services, including 86 deaths; 37 of these deaths did not involve concomitant use of opioid drugs, as reported by Bailey et al. (1990).

17. And, just to underscore that danger, I know of no hospital that permits or condones personnel administering midazolam to patients and then leaving the patients unattended, alone and unmonitored. Even with small doses of midazolam (1-2 mg) patients are always observed and monitored.

18. Midazolam can clearly produce unconsciousness as defined by multiple investigators (Glass et al., 1997; Kuizenga et al., 2001; Reves et al., 1978). Furthermore, midazolam can reduce the amount of a potent inhaled anesthetic (halothane) needed for surgery (Inagaki et al., 1993). Because it is not clinically warranted to administer extremely high doses of midazolam to humans, it is not known if midazolam would produce immobility (in response to noxious stimulation) in humans (as noted above, movement during anesthesia does not necessarily connote consciousness). In mice, however, midazolam can produce complete anesthesia, similar to propofol and sevoflurane, two commonly clinical anesthetics used in humans (Nishikawa et al., 2011). Although the study by Nishikawa et al. focused on mice with genetic alterations, like any such genetic study, normal 'wild-type' mice were also studied for comparison. See Figures 3C and 4C of Nishikawa et al., wherein the loss of the tail-pinch withdrawal response (LTWR) in the normal wild-type mice (WT) lasted a mean = 2250 sec, or about 37 minutes, after midazolam

was administered. Thus, these data support the conclusion that midazolam can act as a complete general anesthetic.

19. One challenge of studying midazolam's effect on consciousness is the large doses that would be required to produce deep unconsciousness. A large dose that would be required to produce deeper levels of unconsciousness would take a long time to wear off and therefore would not be clinically indicated or appropriate. Glass et al. (1997) administered midazolam by infusion and achieved unconsciousness and electroencephalogram depression (bispectral (BIS) levels in the 60s). Because larger doses of midazolam requiring lengthy recovery would have been needed to explore the extent to which midazolam results in deeper unconsciousness, Glass et al. (1997) did not go further. A newer benzodiazepine (remimazolam) is metabolized quickly in humans and thus permits administration of large doses in clinical settings. Antonik et al (2012) found that remimazolam and midazolam could produce deep unconsciousness in some individuals (as demonstrated by a score of 0/5 on the Observer's assessment of alertness and sedation scale, indicating no response to a noxious stimulus). Eisenried et al. (2020) and Schuttler et al. (2020) showed that remimazolam could achieve Narcotrend electroencephalogram levels of 40-60, the range required to perform surgery (for example, see Fig. S7F2 in their supplemental material). These data with remimazolam indicate that benzodiazepines (such as midazolam) in sufficient doses can achieve levels of unconsciousness that would permit otherwise painful procedures.

20. Benzodiazepines (such as diazepam and midazolam) have also been used for the induction of anesthesia (Baker, 1969; Blackmon et al., 1984; Reves et al., 1978; Reves et al., 1985; Kuizenga et al., 2001). I have personally used midazolam to induce anesthesia in patients. Although midazolam is currently not typically used to induce anesthesia, midazolam can be (and

has been) used for that purpose (Blackmon et al., 1984; Reves et al., 1978). The typical induction dose is 0.3 mg/kg, but not to exceed 0.6 mg/kg (see FDA package insert). Additionally, it is important to note that during induction of anesthesia, an endotracheal tube is often placed, which is very stimulating and painful in an awake person. The importance of these studies and reports cited above, relative to the issue of lethal injection using midazolam, cannot be over emphasized: the fact that midazolam by itself might not be the first choice for an otherwise painful clinical procedure does not lessen in anyway its proven ability to be used for such procedures.

21. The study by Crawford et al (1988) adds further to the evidence that midazolam can be used for anesthesia during surgical procedures. In their study, mothers undergoing elective caesarean section received either midazolam or thiopental for induction of anesthesia. Anesthesia was maintained with nitrous oxide (N_2O). What is particularly important to understand is the timing of events during caesarean sections. Unlike most surgical procedures, patients undergoing a caesarean section will be "prepped and draped" while they are awake (prior to anesthesia induction). The surgeon is gowned and gloved, ready with knife in hand. Once the induction drug is administered, the trachea is intubated and following confirmation of the correct placement of the endotracheal tube, the surgeon makes an incision and quickly dissects the underlying tissues. In the Crawford study, N_2O was started soon after the endotracheal intubation, and while N_2O works quickly, I estimate that these patients had midazolam as their primary anesthetic for the first 30-60 seconds of the procedure (see next section for calculations). Meperidine was administered after ligation of the umbilical cord, well after the 30-60 second period being considered here. Crawford et al. (1988) concluded "….midazolam is a suitable alternative to thiopental for induction and maintenance of anesthesia for elective cesarean section".

22. In the Crawford et al. (1988) study, even at high gas flows (such as 10 liters/min), the concentration of N_2O in the brain at 30 sec is estimated to be around 4%, and at 60 sec it is estimated to be around 12%, based on the uptake of N_2O into the respiratory circuit and subsequent uptake into the lungs, and then the vessel rich group, of which the brain is a part. Note: N_2O concentration and partial pressure are used interchangeably. Referring to Figures 4.7 and 12.1 in Eger, (1974), the following calculations provide the estimation of N_2O concentration in the brain: At 10 liters/min inflow, the inspired concentration of N_2O at 30 sec is about 0.45 of the inflow concentration, which was 67% in Crawford et al. (1988). Thus, the inspired N_2O concentration was 0.45 x 67% or 30% at 30 sec. At 60 sec, the inspired N_2O concentration is about 0.75 of the 67%, or about 50%. Turning to Figure 4.7, one sees that the N_2O concentration in the vessel rich group is about 0.24 of the inspired N_2O concentration at 60 sec; extrapolation of the N_2O concentration in the vessel rich group at 30 sec provides an estimate that N_2O concentration is about 0.12 of the inspired N_2O concentration. Thus, at 30 sec, the N_2O concentration in the brain is 0.12 x 0.45 x 67% = 4%, and at 60 sec it is 0.24 x 0.75 x 67% = 12%. These low N_2O concentrations in brain (4% at 30 sec and 12% at 60 sec) are not sufficient to provide any meaningful anesthetic or analgesic effect, as N_2O as high as 45% does not ablate consciousness (Dwyer et al., 1992), and N_2O at 15% does not significantly affect experimental pain (Petersen-Felix et al., 1998). Therefore, the women in the Crawford study who received midazolam for induction had that drug as their only significant anesthetic during the endotracheal intubation, initial incision and dissection of their abdominal tissues. And, it is important to point out that while induction with midazolam, especially in the obstetrical setting, might not be the most accepted clinical approach, midazolam can be used for that purpose.

23. Miyake et al. (2010) examined the effects of midazolam on the electroencephalogram (as

determined by the bispectral number, or BIS) during paralysis and endotracheal intubation. These patients received either 0.2 mg/kg or 0.3 mg/kg of midazolam and were intubated following administration of vecuronium. The patients also received remifentanil, but this opiate was discontinued at the time of intubation, and its effects abate within a few minutes. The patients were left undisturbed for 60 min, and ventilated. No other drugs were administered during this 60 min period. At these single midazolam doses, the BIS readings were in the low to mid- 60s, even though the patients were paralyzed and had an endotracheal tube in place, which is very stimulating. If one were to accept the argument of the plaintiffs, then these patients should have been awake and would have had BIS levels in the 80-90 range (consistent with being awake). And yet, they were not—the BIS levels were in the unconscious range.

24. Midazolam has been used to decrease pain during otherwise painful procedures. Here are examples of human studies of midazolam and its effect on pain:

a. Song et al. (2007): Cystoscopy (involving placement of a rigid or flexible tube into the penis or female urethra.) The authors conclude: "midazolam anesthesia relieved pain during both rigid and flexible cystoscopy" and "Our study indicates that midazolam anesthesia during cystoscopy is well tolerated and is associated with no or minimal discomfort."

b. Turgut et al. (2006): prostate biopsies were performed using midazolam in one group, local anesthesia in a second group and no anesthesia in a third group. The average pain scores (VAS, range 0-10) were 1.4, 2 and 4.7 respectively (the midazolam group having statistically significant lower VAS compared to no anesthesia).

c. Song et al. (2011): Prostate biopsies performed using midazolam

anesthesia or ketorolac, an analgesic drug. In the ketorolac group, 19 of 51 patients reported severe or intolerable discomfort, while only 1 of 53 patients who had received midazolam reported severe or intolerable discomfort.

d. Manning et al., (2016). Midazolam has been used to ablate pain associated with nasogastric tube placement (e.g., a plastic tube inserted into the nose, down the back of the throat and into the stomach). In their paper, Manning et al. wrote "*Patients report that nasogastric tube (NGT) insertion is among the most painful and uncomfortable procedures experiences in the emergency department."* Manning et al. reported that 2 mg midazolam reduced the pain score from 52 to 21 (on a 0-100 scale). Furthermore, they wrote "*Several ED clinicians felt that use of midazolam prior to insertion was superior to topical anesthetic alone and did not want their patients randomized into the study (where they could potentially receive placebo)"*

e. Nakanishi et al. 1997: These authors administered midazolam at different doses and tested responses to painful stimuli applied to the face. The authors report "we found that midazolam in clinically appropriate doses not only acts as a sedative, but also reduces the sensitivity of the labial region to pain."

f. Cinar et al. (2009): Midazolam used for colonoscopies.

g. Chen et al. (2017): A meta-analysis showing intra-articular injection of midazolam reduces pain following knee arthroscopies.

25. There is ample data which indicates that midazolam can be used to render an inmate

insensate to the pain produced by the second and third execution drugs. Three studies are informative. White (1982) compared midazolam (0.3mg/kg) to thiopental (4mg/kg) and ketamine (1.5mg/kg) to induce anesthesia using a rapid sequence induction technique. White did not check for consciousness, and administered succinylcholine (a paralytic) with the induction drugs (in the midazolam group, only 3 of 20 patients had received narcotic analgesics within 4 hours of the induction, a small percentage, similar to those in the other groups). The patients were then intubated. He reported heart rate and blood pressure changes and found that, after intubation, the heart rate and blood pressure increases in the midazolam group were no different from the group that had received thiopental, which is a complete anesthetic (see his Table 2).

26. Michaloudis et al. (1996) reported similar findings to White (1982). The heart rate increase from immediately before to immediately after intubation was, on average, about 10 beats per minute in the midazolam group (0.4 mg/kg intravenously), but was about 14 beats per minute in the Propofol group (see their Table 2). Of note, propofol is a complete anesthetic. My statistical analysis of the reported means and standard deviations showed no significant differences in heart rate or blood pressure between the midazolam and propofol groups at any time (using unpaired t-test and correcting for multiple comparisons).[3]

27. Isoflurane, which is a complete anesthetic, does not blunt the heart rate and blood pressure response to intubation. Intubation is very stimulating, and the isoflurane concentration required for intubation is about 40% greater than that needed to blunt motor responses to skin incision (Zbinden et al., 1994a). Yet, even at these high isoflurane concentrations (around 1.9%

3 Michaloudis et al. gave intramuscular midazolam to all patients and reported the dose at 0.8 mg/kg in methods, but 0.08mg/kg in the abstract. I believe the latter dose to be correct, and the former to be an error, as it represents a dose well beyond the clinical range. In addition, an intramuscular dose = 0.08mg/kg is consistent with dosing guidelines in the package insert. In any case, the use of intramuscular midazolam does not negate the overall conclusions.

end-tidal) the heart rate increased 36 beats per minute and systolic blood pressure increased 49 mmHg with intubation (see their Figure 2 and Figure 3) (Zbinden et al., 1994b). In the Kazama (1997) study, propofol was used alone in one group. Similar to the Zbinden study, there were marked increases in heart rate (17 beats/min) and systolic blood pressure (about 23 mmHg) with intubation, even though the propofol concentration was about 50% greater than that needed to prevent movement in response to skin incision. The fact that midazolam blunts the cardiovascular response to intubation more effectively (White, 1982; Michaloudis et al., 1996) relative to isoflurane, suggests that patients given induction doses of midazolam (0.3-0.4 mg/kg) are well anesthetized.

28. The table below is from White (1982). Note that the change in blood pressure (mean arterial pressure, MAP) and heart rate (HR) is from baseline (prior to drug administration).

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TABLE 2. Cardiovascular Effects Following Rapid Intravenous Administration for Induction of General Anesthesia*

Drug Group	Dosage (mg/kg)	Baseline		Induction†		Intubation†	
		MAP (mmHg)	HR (BPM)	ΔMAP (%)	ΔHR (%)	ΔMAP (%)	ΔHR (%)
Thiopental	4.0	99 ± 4	104 ± 4	−11 (±2)	+11 (±2)	+36 (±6)	+22 (±4)
Ketamine	1.5	97 ± 2	101 ± 3	+10 (±1)‡	+11 (±2)	+34 (±5)	+34 (±4)‡
Midazolam	0.3	95 ± 2	101 ± 4	0 (±2)‡	+10 (±2)	+34 (±4)	+24 (±4)
Midazolam/Ketamine	0.15/0.75	97 ± 3	109 ± 5	+2 (±2)‡	+5 (±1)‡	+31 (±4)	+17 (±4)

* Values are means ± SEM.
† Values represent percentage change from baseline.
‡ Differed significantly from thiopental group, $P < 0.05$.

Using the baseline MAP and HR, and the percent change in those parameters, the average data can be determined and are shown below.

	Baseline		Induction		Intubation	
	MAP	HR	MAP	HR	MAP	HR
Thio	99	104	88	115	135	127
Ket	97	101	107	112	130	135
MDZ	95	101	95	111	127	125
MDZ/Ket	97	109	99	114	127	128

Importantly, just as in the Michaloudis study, we must look at the change from induction values to intubation values. Note that, in the midazolam group, the MAP changes from 95 mmHg to 127mmHg, while it is from 88 mmHg to 135 mmHg in the thiopental group. At the very least, the midazolam group (127 – 95 = 32) value is numerically lower than that of the thiopental group (135 – 88 = 47). The heart rate differences (127-115 = 12 for thiopental vs. 125-111 = 14 for midazolam) are similar.

29. The following questions arise when considering these studies (White, 1982; Michaloudis et al., 1996) : if midazolam at doses of 0.3 mg/kg (White study) and 0.4 mg/kg (Michaloudis study) was insufficient to render the patients unconscious and insensate, why were the heart rate and blood pressure changes not higher (indeed, much higher) when compared to changes occurring in patients administered complete anesthetics (e.g., isoflurane, Zbinden et al., 1994b)?[4] Importantly, the physiological maximal heart rate in these patients is probably around 180-200 beats per minute, so the patients were capable of much greater heart rates. The answer, in my opinion, to a reasonable medical and scientific certainty, is that midazolam administered to

4 Increases in heart rate and blood pressure are common during surgery and even deep levels of anesthesia do not ablate these increases. In fact, even brain dead humans can have marked increases in blood pressure and heart rate during organ donation.

persons at doses of 0.3-0.4 mg/kg, as reported and described in the package insert (and at greater doses, including 500 mg), produces unconsciousness, blunts responses to noxious stimuli, and reduces awareness of pain, such that these persons do not experience pain any more than persons anesthetized with other anesthetics such as thiopental, propofol or isoflurane.

30. Endotracheal intubation is markedly stimulating and painful in an awake individual, as it involves placing a large plastic breathing tube through the mouth into the trachea (windpipe). In fact, in terms of anesthetic requirements, endotracheal intubation requires more anesthesia than is needed for a surgical incision (Zbinden et al., 1994a). Gehrke et al. (2015) studied patients in the intensive care unit who required endotracheal intubation. One group of patients received midazolam (mean dose 15 mg, range 10-17.5 mg); at least 12 of 17 patients in the midazolam group did not receive other drugs (such as opioids). The authors concluded "…intubation using….midazolam is highly effective and well tolerated…." (Gehrke et al., 2015).

31. Anesthesiologists routinely observe patients in the OR who are being ventilated, with little or no other stimulation, who then react violently to the endotracheal tube, as exhibited by coughing and "bucking" against the ventilator. Indeed, this is why patients in the ICU often receive sedation during mechanical ventilation, often with midazolam (Somma et al. 1998; Zomorodi et al. 1998). Quoting from the introduction of Somma et al.: "Inadequate sedation during controlled ventilation may lead to increased cardiopulmonary and metabolic demands, resulting in hypertension, tachycardia, arrhythmia, myocardial ischemia, tachypnea and hyperventilation."

32. Five-hundred (500) mg of midazolam administered intravenously to a human is about 100-200 times the normal therapeutic dose and about 10-20 times the dose recommended to induce general anesthesia. Based on the references cited above and my own experience, it is my

opinion, to a reasonable degree of medical and scientific certainty, that a person given 500 mg midazolam would be rendered completely unconscious and insensate to pain and noxious stimuli. Therefore, it is my opinion, to a reasonable degree of medical and scientific certainty, that there is only an exceedingly small risk that a person administered a 500 mg dose of midazolam would experience any pain (conscious awareness of noxious stimulation) as a result of a surgical or medical procedure, or the administration of drugs, including paralytic drugs (such as vecuronium bromide, rocuronium bromide, pancuronium bromide) and potassium chloride. Furthermore, it is my opinion, that 500 mg of midazolam would produce a state of anesthesia comparable to levels of anesthesia considered adequate and sufficient for otherwise noxious and painful medical procedures performed on a daily basis across the United States and the world. Midazolam, by itself, might not be the first choice clinically, but that does not detract from its effectiveness in these settings. The main reason midazolam by itself is not used is because a large dose would be required, which would result in delayed recovery and discharge.

Pulmonary edema in executed inmates

33. I am familiar with claims that autopsies performed on inmates who were executed with lethal injection with midazolam and pentobarbital showed lung congestion and pulmonary edema. The presence of pulmonary edema is a common finding in drug overdose (Mijatovic et al., 2014; Chen & de Jong, 2017; Pelltier & Andrew, 2017). Furthermore, midazolam, as administered according to the Oklahoma protocol, will produce unconsciousness well before the full 500 mg dose is administered. The dose needed for induction of anesthesia is about 0.2-0.6 mg/kg. For a 100-kg person, that corresponds to a dose = 20-60 mg. Thus, when about 10% of the 500 mg dose of midazolam is administered, the inmate will have received sufficient

midazolam to become unconscious. Pulmonary edema, even if it occurs immediately ante-mortem, would not be sensed by the inmate who has received midazolam. In fact, benzodiazepines are considered by some to be a treatment to relieve the anxiety produced by pulmonary edema (Bosomworth, 2008), and midazolam is the subject of a registered clinical trial for that purpose (Dominguez-Rodriguez et al. 2017; see also https://clinicaltrials.gov/ct2/show/NCT02856698?term=midazolam&cond=Pulmonary+Edema&draw=2&rank=1 accessed 1-15-2021) .

34. More recent studies in humans using post-mortem computed tomography (PMCT) show that fluid accumulates in lung over time in the post-mortem period (Shiotani et al., 2011). Shiotani et al. write in their concluding paragraph: "PMCT findings of the lung are not fixed and change with the passage of time after death in accordance with progression of postmortem changes (pulmonary congestion and edema) in the corpse."

35. Likewise, fluid accumulation in the airways increases during the post-mortem period (Ishida et al. 2014); these authors showed that fluid accumulated in the airways (main bronchi) as the interval between death and PMCT increased. This fluid accumulation is akin to the fluid that has been found at autopsy in inmates executed by lethal injection.

36. Published data on how post mortem pulmonary edema and lung congestion occur and progress is based in large part on animal studies. Durlacher et al. (1950) examined post mortem changes in rabbit lung after various causes of death, including pentobarbital overdose. They found that lung weight increased as the time between pentobarbital-induced death and autopsy increased, as shown in their table 2:

TABLE 2

EFFECT OF INTERVAL AFTER SACRIFICE BY NEMBUTAL (100 MG./KG.) ON LUNG WEIGHT

Interval after sacrifice	*Treatment*	*Number of animals*	*Lung weight per kilo ± S.E. mean*
			Grams
Immediate		5	3.83 ± .27
1 hours	Cannula in trachea	5	5.42 ± .58
2 hours	Cannula in trachea	5	7.09 ± 1.39
3 hours	Cannula in trachea	19	9.46 ± .62
4 hours	Cannula in trachea	5	10.88 ± 1.53
6 hours	Cannula in trachea	5	10.95 ± .74

Note that lung weight increased when comparing lung weight at immediate autopsy to lung weight at 1, 2, 3, 4 and 6 hours after death, indicating that lungs can develop edema *after* death. These researchers (and others[5]) also found that, for a variety of causes of death, lung weight increased as the interval between death and autopsy increased (see table 1 in Durlacher et al., 1950). These data indicate that post mortem edema formation is a generalized phenomenon and is not specific to drug overdose. Notably in the Durlacher et al. study (their table 2 above), the ratio of the heaviest lung weights (at 6 hours) to the lung weight at immediate autopsy is 2.86 (10.95/3.83), which is a nearly 200% increase, similar to the increased lung weights found at autopsy in inmates executed by lethal injection. Thus, the animal data indicate that all of the pulmonary edema and lung congestion found at autopsy in inmates executed by lethal injection could be generated post-mortem.

37. Symptoms of pulmonary edema vary, and many people with pulmonary edema are asymptomatic. Large portions of patients with pulmonary edema due to renal failure, re-expansion pulmonary edema and high-altitude pulmonary edema report no symptoms (Mallamaci et al., 2010; Enia et al., 2013; Marino et al., 2015; Bouzat P et al., 2013; Devine

5 See Acta Scandinavica Medica 1964 in References Cited

2014; Kim et al., 2009; Baik et al., 2010). These data indicate that pulmonary edema and lung congestion do not necessarily go hand-in-hand with sensations of breathlessness.

38. Frothy fluid and foam are sometimes found in humans and animals after death, and there is evidence that this froth can occur immediately prior to death (in the period from apnea to cardiac death; see Swann 1964) and after death.[6] Thus, the finding of froth in inmates who were executed by lethal injection does not indicate that this froth was generated ante mortem.

39. Post mortem froth and foam could be generated by the release of gasses from the lung tissues and interacting with the lung surfactant, a substance that, during life, keeps alveoli (small lung units, or air sacs) open. Related to this issue, Pattle (1955) wrote that "….oedema foam is thus not produced by agitation of the oedema fluid with air during respiration; it can only have been formed by air originally in the fine air spaces of the lung being broken up into bubbles and afterwards expelled into the bronchi and trachea." Thus, the post mortem finding of froth in inmates who were executed by lethal injection does not necessarily indicate that this froth was generated ante mortem, or by conscious attempts to breathe.

40. Midazolam is not likely to produce pulmonary edema via an "acid" effect. The total amount of hydrogen ion administered with 500 mg midazolam is about 2-3 mEq,[7] which will be given over the approximately 2 minutes of administration.[8] Thus, there is ample time for the midazolam and its carrier to mix with blood as it enters the pulmonary vasculature; blood has a

6 Animals (rabbits) made uremic (kidney failure) and who subsequently developed pulmonary edema were found to not only have increasing lung weights as the period between death and post mortem exam increased, but the presence of froth was found in animals that had later post mortem exams, while none was found upon immediate post mortem examination. See Acta Scandinavica Medica 1964 in References Cited

7 Depending on the pH, midazolam will have up to two hydrogen ions bound to each midazolam molecule (Gerecke, 1983), and 0.5 grams (500mg) divided by the molecular weight of 326 g/mole yields about 3 mEq of H+; the pH = 3 yields 0.1 mEq of H+ based on 100 ml of midazolam solution

8 Based on midazolam concentration of 5mg/ml, and injection rate of about 1 ml/sec.

significant buffering capacity that will counteract the addition of this small amount of hydrogen ions (Ellison et al., 1958).

41. Midazolam, despite being in an acidic solution, is not painful on intravenous administration (Reves et al., 1985; Dundee at al., 1980). Furthermore, midazolam enjoys this property of "painless" injection relative to other intravenous anesthetic drugs (such as etomidate and propofol; Vuyk et al., 2019).

42. Studies indicate that fluid in the lung (as would occur with pulmonary edema) is not so stimulating that it would cause an anesthetized person to become aware and to suffer. There is a procedure which is performed in patients that involves—literally—pouring fluid into a patient's lung. The procedure is called whole lung lavage and it is used for patients who have pulmonary alveolar proteinosis. I have provided anesthesia for multiple patients undergoing this procedure.

43. As described by Smith et al. (2019) general anesthesia using either an inhaled anesthetic (such as isoflurane, sevoflurane) or intravenous anesthesia (such as propofol and an opiate) can be used for whole lung lavage. Once the patient is anesthetized, a specialized endotracheal tube (double lumen tube) is inserted into the patient so that one lung can be ventilated separate from the other lung. Fluid (usually saline) is then poured into the non-ventilated lung, drained out, and more saline is poured into the lung. According to the experience of Smith et al. (2019) up to 1 liter of saline is placed into the lung, drained 2-5 minutes later, and the process repeated. Over the course of several hours as much as 50 liters of saline are instilled per lung (Abdelmalak et al., 2015). Whole lung lavage is akin to profound 'pulmonary edema' yet there is no indication that patients awaken during the procedure. For all the reasons stated above, even if midazolam did cause pulmonary edema ante mortem the subject would be sufficiently anesthetized such that the subject would not experience the sensation associated with pulmonary edema.

44. Plaintiffs cite various eye-witness reports that describe movements by inmates after administration of midazolam. These movements (lurching, heavy breathing, gasping, coughing, etc.) most likely represent breathing efforts of an unconscious person, similar to what occurs in people who snore heavily. Most importantly, these movements do not likely represent conscious awareness. Midazolam can cause upper airway collapse (similar to what occurs with sleep-induced airway collapse that leads to snoring) (Montravers et al., 1992); these authors reported that "a sedative dose of midazolam produced a marked increase in upper airways resistance". These various breathing patterns are commonly observed during anesthesia and represent partial airway obstruction. Anesthesiologists are familiar with the 'rocking boat' breathing pattern, in which a patient has paradoxical movement of the chest and abdomen during attempts to breathe (Wilson & Benumof, 2007). These breathing patterns are well-described in anesthetized patients and do not represent an awake person struggling to breathe.

The Ceiling Effect

45. Although much has been made of the "ceiling effect" and its relationship to midazolam and barbiturates (such as thiopental and pentobarbital), the so-called ceiling effect cannot be accurately and reliably determined by extrapolation from a variety of laboratory studies. As noted by the Supreme Court in this case, the mechanism or existence of a ceiling effect is not important, only when any ceiling effect "kicks in". I would add that it also matters what end-point is being discussed. Indeed, discussions of anesthetic action must always include what end-point of unconsciousness is being examined. In my opinion, deep coma-like unconsciousness (as produced by high anesthetic doses) is not needed to ensure lethal injection does not pose a significant risk of severe pain. Deep, coma-like unconsciousness (as demonstrated by a severely

depressed electroencephalogram) is generally not sought during anesthesia and surgery, and, in fact, is avoided. Thus, most surgery occurs during periods when the brain, albeit depressed, is still active, as demonstrated by the electroencephalogram, and the vast majority of patients are not conscious and have no recall or memory of surgery. The relevant "ceiling" for these purposes is unconsciousness to the point that the inmate perceives no severe pain from the effects of the injected drugs, and by that definition, midazolam exceeds that relevant ceiling. Furthermore, calculating a ceiling effect by extrapolation from various basic science studies is fraught with uncertainty, especially when considering the different experimental conditions that are used (different cells, different temperatures, etc.) and the inherent variability of results.

46. The discussion of the mere existence of a potential ceiling effect thus obfuscates the issues. The primary medical and scientific issue raised is whether the ceiling effect, if it exists for midazolam, occurs before a person becomes unconscious and insensate to any pain and noxious stimuli caused by the execution drugs. In other words, the relevant question is whether at the point which the ceiling effect is reached, will a person who has been administered a 500 mg IV dose of midazolam be at a level of unconsciousness where he cannot feel noxious stimulation associated with the administration of execution drugs? It is my opinion based on the references cited above, that any purported ceiling effect does not affect midazolam's ability to induce unconsciousness and render a person insensate to pain and noxious stimuli associated with Oklahoma's execution protocol. Furthermore, a 500 mg IV dose of midazolam would be expected to produce that clinical and pharmacological effect for a longer time, when compared to a smaller dose.

47. None of the studies I have seen cited in my experience with execution cases justifies the view that midazolam has a ceiling effect that will prevent it from rendering an inmate

unconscious and insensate to any pain that might be caused by the drugs used in the Oklahoma execution protocol. Notwithstanding any arguments about the 500 mg midazolam dose and a ceiling effect, the large dose does provide a pharmacokinetic advantage in that the drug concentration in the effect site (brain) will be quite high for a long period of time, certainly up to the point of death. This high concentration assures us that there is no concern that the inmates would awaken from a falling drug level. Indeed, the data from the Miyake et al. (2010) study suggest that even small doses of midazolam are sufficient to maintain unconsciousness for 60 minutes.

Actions of Vecuronium and Potassium

48. Vecuronium will paralyze muscle, including the diaphragm, the muscle of breathing, which will stop breathing and result in the build-up of carbon dioxide. However, this increased amount of carbon dioxide is not sufficient to awaken anesthetized patients (Naguib et al, 2005). How "painful" is drug-induced diaphragm paralysis and apnea, such as that caused by the second drug in the Oklahoma protocol? Heirer et al. (2001) performed a study similar to the Naguib study. Heier used thiopental and succinylcholine (a paralytic), which caused apnea for about 5 min, on average (range 3.5 to 9 min). Seven of 12 volunteers had awareness during apnea, and 5 of these 7 reported "emotional distress" because of the strong urge to breathe. How distressful was this urge to breathe? Tellingly, the authors reported "All of the volunteers stated that they would participate in a second similar study if asked to do so." Obviously, the distress was not so much that any volunteer would not have done the study again. And, the ethics committee approved the Heier study and volunteers participated with the full knowledge that awake paralysis was a possibility.

49. Intravenous administration of potassium is painful in the awake person, but midazolam at

500 mg would render the inmate unconscious and unable to experience pain from potassium, as described above. While intravenous infusion of potassium is painful in awake and conscious patients there is no evidence that it is a supramaximal stimulus, as described above, or that its use in a person rendered unconscious by anesthetic drugs, including midazolam, would result in that person awakening.

50. If movement did occur during midazolam-induced unconsciousness, such movement cannot be assumed (and is not likely) to be the actions of a conscious person (as noted above). Furthermore, rocuronium, a drug commonly used after anesthetic induction to produce muscle paralysis, is associated with movement in many human subjects immediately after intravenous administration (prior to the onset of paralysis) (Joo et al., 2014; Kim et al., 2006); such movement has been associated with vecuronium as well. This movement is thought to be secondary to vein irritation. Yet there is no evidence that it causes awakening. Indeed, the processed electroencephalogram (bispectral number, or BIS) does not change when the drug is given, despite the movement occurring (Joo et al., 2014), indicating that presumed vein irritation does not alter anesthetic-induced unconsciousness.

Training and experience of execution team members

51. Oklahoma's lethal injection protocol specifies that qualified personnel will implement the execution protocol, including licensed physicians, nurses, EMTs, paramedics, physician assistants. Such individuals, by nature of their education, training and experience, would have experience and knowledge of the various functions required for the execution protocol, including drawing up drugs into syringes, application of electrocardiogram electrodes, monitoring of the electrocardiogram, placement of intravenous lines (and monitoring the patency and integrity thereof) and injections of drugs. Non-physicians, such as nurses and paramedics, are capable of

determining levels of consciousness (Davis et al., 2006; Dreyfus et al., 2017). In fact, nurses in the ICU, following physician orders, often titrate drugs such as midazolam and propofol based on their evaluation of the level of consciousness in the patient.

52. Non-physicians are clearly capable and trained to determine levels of consciousness. Paramedics are trained in the use of the Glascow Coma Scale, nurses are trained in the use of the Richmond Sedation scale and Glascow Coma scale. In my clinical practice, and my experience watching many other anesthesiologists, it is actually uncommon for an anesthesiologist to do more than verbal consciousness checks after induction, but prior to laryngoscopy and intubation, which are excruciatingly painful in the awake person. In fact, during a rapid-sequence induction, no consciousness check might occur—the drugs are administered and the trachea quickly intubated without any consciousness check whatsoever. Koerber et al. (2009) reported that many anesthesia providers do not check for unconsciousness after the induction drug and before giving the neuromuscular blocking drug (see their Table 4: only 54% of providers always wait for loss of consciousness before administering a neuromuscular blocking drug).

53. Medically appropriate consciousness checks performed by members of the execution team following administration of the midazolam are sufficient to determine whether the condemned inmate has been rendered sufficiently unconscious as to be unaware of any pain produced by administration of the paralytic drug and the potassium chloride. The American Society of Anesthesiologists practice advisory (2018) includes clinical signs (such as verbal and tactile stimuli) as ways to assess consciousness. Furthermore, a reflex withdrawal (in response to noxious stimulation) is NOT considered purposeful movement (footnotes on pages 438, 442, 443, 450; Table 1 page 463 of the advisory).

Proposed Alternate Method of Firing Squad

54. In regard to execution by firing squad, individuals who are shot through the chest, with the bullets exiting the back and shattering the spine, would not survive. But, for the 8-10 seconds of consciousness after bullet entry, the injury would be severely painful, especially related to shattering of bone and damage to the spinal cord. As an example of the injuries that occur from the firing squad, see the recording of the execution of Anton Dostler, a German general in World War II. In one camera angle, bullets exit through his back and through the wooden post to which he is tied (https://www.youtube.com/watch?v=d0lRSxAPdpM&t=365s accessed 1-14-2021). Furthermore, not all firing squad executions go 'smoothly': see the execution of two men in Guatemala in which both men initially survive the volley of bullets and are subsequently killed by shots to the head (https://www.youtube.com/watch?v=6Ugd6UgLlXM accessed 1-14-2021). Finally, just as we cannot ask an inmate executed by lethal injection whether the process was painful, so too we cannot ask the same question of an inmate executed by firing squad. In my opinion, execution by firing squad would not significantly reduce the risk of severe pain that Plaintiffs claim is inherent in the Oklahoma execution protocol.

55. Any pain and suffering that an inmate might experience as a result of the Oklahoma execution protocol can be compared to other previously used methods of execution, including hanging (see Hillman 1993 for review). Despite the intended outcome of cervical fracture, severing of the spinal cord and a 'quick' death, judicial hangings have often resulted in deaths without cervical fracture and slow strangulation. In a series of 34 executions by hanging, only 6 condemned prisoners had cervical fractures (James & Nasmyth-Jones, 1992). Hanging can cause death by asphyxia. And, even if there is severing of the spinal cord, nerve impulses (such as those arising from the neck, head and face) can be transmitted to the brain via intact pathways

above the injured spinal cord, leaving the inmate to experience the resulting pain during the asphyxiation process.

Conclusion

56. It is my opinion, to a reasonable degree of medical and scientific certainty, that 1) Midazolam administered at 500 mg will render an inmate unconscious; 2) the inmate will not perceive or feel pain related to the administration and actions of midazolam, vecuronium and potassium; 3) any pulmonary edema that occurs ante mortem will not be perceived by the inmate; 4) the IV Team professionals specified in the Oklahoma lethal injection protocol have, as a general matter, adequate training to perform their roles as specified in the protocol; 5) execution by firing squad would not significantly reduce the risk of severe pain as compared to lethal injection; 6) execution by older methods (such as hanging) likely result in pain.

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Zbinden AM, Maggiorini M, Petersen-Felix S, Lauber R, Thomson DA, Minder CE. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. Anesthesiology. 1994a; 80:253-60.

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Zomorodi et al. Population pharmacokinetics of midazolam administered by target controlled infusion for sedation following coronary artery bypass grafting Anesthesiology 1998; 89:1418-29

CURRICULUM VITAE
Joseph F. Antognini, M.D., M.B.A.

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EDUCATION:

1980	University of California, Berkeley (B.A., Economics)
1984	University of Southern California (M.D., Medicine)
2010	California State University, Sacramento (M.B.A., Business)

INTERNSHIP/RESIDENCY:

1984-1987	Anesthesiology, UC Davis Medical Center
1986-1987	Chief Resident

PROFESSIONAL POSITIONS:

1/20-present	Adjunct Faculty Los Medanos College Pittsburg, CA
1/20-5/20	Adjunct Faculty Holy Names University Oakland, CA
9/16-11/19	Physician Surveyor The Joint Commission Oakbrook Terrace, IL
7/17-present	Director Emeritus University of California, Davis
2011-2020	Clinical Professor of Anesthesiology and Pain Medicine (Volunteer Clincal Faculty appointment) University of California, Davis—School of Medicine
11/10-6/16	Director of Peri-operative Services UC Davis Health System
7/00-7/11	Professor of Anesthesiology and Pain Medicine (with tenure)

	Department of Anesthesiology and Pain Medicine University of California, Davis—School of Medicine
12/02-7/11	Professor of Neurobiology, Physiology and Behavior (with tenure; WOS appointment) College of Biological Sciences University of California, Davis
11/98-7/10	Vice Chairman, Director of Research
11/98-3/02	Director of Malignant Hyperthermia Diagnostic Laboratory Department of Anesthesiology
7/96-7/00	Associate Professor (with tenure) Department of Anesthesiology University of California, Davis—School of Medicine
10/91-6/96	Assistant Professor Department of Anesthesiology University of California, Davis—School of Medicine
7/87-9/91	Staff Anesthesiologist (Private Practice) American River Hospital Department of Anesthesiology Carmichael, CA
7/87-9/91	Assistant Clinical Professor (volunteer) Department of Anesthesiology University of California, Davis—School of Medicine

LICENSURE & CERTIFICATIONS:
State of California #G55662 (active)
Diplomate, National Board of Medical Examiners (1985)
Diplomate, American Board of Anesthesiology (1989)
Certificate of Recertification, American Board of Anesthesiology (1999, 2009)
Certified Yellow Belt, 2017

PROFESSIONAL SOCIETIES AND RECOGNITION:
American Society of Anesthesiologists 1987--present
California Society of Anesthesiologists 1987—present
Fellow of the American Society of Anesthesiologists 2018—2019

ADVOCACY
ASA Grassroots Network (ASA Team 535) 2018

ASAPAC Donor—2018
FAER Donor—1999-2019

RESEARCH INTERESTS:
Mechanisms of anesthesia; factors influencing anesthetic requirements; OR efficiency

AWARDS AND HONORS
Dean's Mentoring Award, UC Davis School of Medicine, 2006
Associated Students of UC Davis "Excellence in Education Award" College of Biological Sciences, 2007
Associated Students of UC Davis "Excellence in Education Award" Outstanding Educator, 2007
Foundation for Anesthesia Education and Research, Mentor Academy, 2008
Phi Kappa Phi Honor Society, 2010

GRANTS
1. UC Davis Faculty Research Grant 1991-92—The effect of intrathecal aspirin on anesthetic requirements in rabbits, $2500
2. UC Davis Faculty Research Grant 1993-94—Validation of a preferentially anesthetized goat brain model, $1500
3. Foundation for Anesthesia Education and Research 1994—Determination of gross anatomic sites of anesthetic action, $25,000 ($25,000 matching departmental funds)
4. UC Davis Faculty Research Grant 1994-95—The effects of general anesthesia on cerebral blood flow patterns as assessed by functional magnetic resonance imaging, $1500
5. UC Davis Faculty Research Grant 1996-97—The effect of differential isoflurane delivery to brain and spinal cord on inhibitory and excitatory output from the brain, $10,000
6. Foundation for Anesthesia Education and Research 1997-99—The effect of differential isoflurane delivery to brain and spinal cord on inhibitory and excitatory output from the brain, $70,000 ($70,000 matching departmental funds)
7. NIH R01 GM57970 Brain and Spinal Cord Contributions to Anesthetic Action 8/98-4/02 (Priority Score 120, Percentile 1.0). Total costs $713,026
8. NIH R01 GM61283 Anesthetic Effects on Sensorimotor Integration 2/01-2/06 (Priority Score 194, Percentile 16.9). Total costs $672,791
9. U.C. Davis Faculty Research Grant. Indirect effect of isoflurane and lidocaine on EEG activation. 7/1/01-6/30/02, $4,000
10. NIH R01 GM57970-4A1 Brain and Spinal Cord Contributions to Anesthetic Action 4/02-12/05 (Priority Score 197, Percentile 20). Total costs $1,284,689
11. NIH 3R01GM057970-05S1 Brain and Spinal Cord Contributions to Anesthetic Action. Minority Supplement grant. 7/03-7/04. Total costs $55,932
12. NIH P01 GM47818 Anesthetic Effects on Spinal Nociceptive Processing 8/04-7/09 (Priority Score 185). Total costs $804,325

13. NIH R01 GM61283A1 Anesthetic Effects on Sensorimotor Integration 12/05-12/9 (Priority Score 158, Percentile 9). Total costs $748,432

TEACHING

Post-Graduate:

1. Resident lectures on neuroanesthesia, anesthetic mechanisms, malignant hyperthermia, neuromuscular blocking drugs, volatile anesthetics, anesthesia research. 1991-2019
2. Anesthesiology Department Journal Club 2013-2016
3. UCSF Changing Practice of Anesthesia—Faculty. September 2014: Peri-operative Medicine and Healthcare Reform: Challenges and Opportunities for Anesthesiology

Graduate:

Guest lecturer for NPB 219 (E. Carstens, Instructor). 1998-2003
Guest lecturer for NPB 112 (E. Carstens, Instructor). 2001-2008
Guest lecturer for first year medical students—pain physiology 2002-2003
Facilitator, Application of Medical Principles 2002-2008
Guest Lecturer, 210B (Systemic Physiology) January 2006
Instructor of Record, Applied Physiology and Pharmacology 2007, 2008

Undergraduate:

NPB 10—Elementary Human Physiology (4 units). 2001-2009
Freshman Seminar: The Supreme Court and You. (2 units) 1998-2010

MENTORED STUDENTS, RESIDENTS AND POST-DOCTORAL SCHOLARS

1.	Kevin Schwartz, M.D.	Resident	1993
2.	Michael Borges, M.D	Resident	1994
3.	Agi Melton, M.D.	Resident	1994
4.	Etsuo Tabo, M.D.	Post-Doctoral Scholar	1997
5.	Steven Jinks	Graduate Student	1998-2001
6.	Chris Simons	Graduate Student	1998
7.	Xiao Wei Wang, M.D.	Post-Doctoral Scholar	1999
8.	Xiaoguang Chen, M.D.	Post-Doctoral Scholar	2000
9.	Makoto Sudo, M.D.	Post-Doctoral Scholar	2000
10.	Satoko Sudo, M.D.	Post-Doctoral Scholar	2000
11.	Alison Fitzgerald	Undergraduate Student	2000-2001
12.	Andrew Hall	Undergraduate Student	2001
13.	John Martin, M.D.	Resident	2001
14.	Steve Jinks, PhD.	Post-Doctoral Scholar	2001-2004
15.	Jason Cuellar, BS	Graduate Student	2003-2004
16.	Linda Barter, MsVM	Graduate Student	2004-2007
17.	Mashawn Orth	Graduate Student	2004-2005
18.	Carmen Dominguez, MD	Assistant Professor	2003-2005
19.	Lauire Mark	Undergraduate Student	2005, 2006
20.	Matthew LeDuc	Medical Student	2005

21. Toshi Mitsuyo, M.D.	Post-Doctoral Scholar	2004-2005
22. Kevin Ng, M.D.	Resident	2005-2006
23. JongBun Kim, M.D.	Post-Doctoral Scholar	2006
24. Sean Shargh	Undergraduate Student	2006-2007
25. Aubrey Yao, M.D.	Resident	2006-2007
26. Alana Sulger	Undergraduate Student	2006-2007
27. Gudrun Kungys, M.D.	Resident	2007-2008
28. Jason Talavera	Medical student	2007
29. Onkar Judge	Medical student	2008
30. Andrew Cunningham	Undergraduate Student	2008
31. Lauren Boudewyn	Undergraduate Student	2008
32. Austin Kim	Undergraduate Student	2008
33. Jason Andrada	Graduate Student	2009-2010
34. Jun Ye	Graduate Student	2014-2015
35. Reihaneh Forghany	Resident	2018-2019

SPECIAL ACTIVITIES:

Staff Anesthesiologist, American River Hospital, 1987-1992
Medical Advisor, CMT International (Charcot-Marie-Tooth), 1991-2000
Director, Case Conferences, Department of Anesthesiology, April-June, 1992
Proctor, Medical Board of California, 1992
Staff Membership, Sutter Davis Hospital, Davis, CA, 1992-1995
Consultant, Malignant Hyperthermia Hotline, Malignant Hyperthermia Association of the United States (MHAUS), 1992-2002
Associate, UC Davis Diagnostic Malignant Hyperthermia Laboratory, 1992-2010
Member, Subcommittee on Experimental Neuroscience and Biochemistry, American Society of Anesthesiologists, 1996
Finance and Executive Committees, UC Davis Department of Anesthesiology, 1996-2002
Quality Assurance Committee, U.C. Davis Department of Anesthesiology, 1998-2004
Course Director, Annual U.C. Davis Anesthesiology Update (CME meeting), 1996-2003
California Society of Anesthesiologists: Educational Programs Committee, 1998-2000
Coordinator, Grand Rounds, Department of Anesthesiology, 1996
Professional Billing Workgroup, U.C. Davis, 1996-98
Question Writer, American Board of Anesthesiology, 1998-2001
Member, UC Davis Animal Care Committee, 2000-2003
Member, UC Davis School of Medicine Personnel Committee, 2003—2007; Chair 2007
Member, UCD Committee on Academic Personnel (Appellate Sub-committee) 2009-11
Management Advisory Committee, Department of Anesthesiology, 2007
Ad Hoc Reviewer for *Anesthesiology, Hospital Topics, Journal of Clinical Anesthesia, Journal of Comparative Neurology, Regional Anesthesia and Pain Medicine, Pain, Brain Research, Journal of Neuroscience, Anesthesia and Analgesia, British Journal of Anaesthesia, Neuroscience, Cephalgia, Neuroscience Letters, Jounral of Chromatography, Basic & Clinical Pharmacology & Toxicology, Therapeutics and Clinical Risk Management.*

Member, VA Merit Review Subcommittee, Alcohol and Drug Dependence, 2002-2005
Editor, American Board of Anesthesiology/ American Society of Anesthesiologists In-Training Examination 2003-2008
Associate Editor, *Anesthesiology* 2005—2011
Faculty Execuitve Committee, School of Medicine 2009-2010
Chair, Faculty Execuitve Committee, School of Medicine 2010-2011
Member of various hospital committees 2011-2016: Medical Staff Executive Committee, Quality Safety Committee, OR Committee, Surgical Services Steering Committee

BIBLIOGRAPHY

EDITED BOOKS

1. Antognini JF, Carstens EE, Raines DE. Neural Mechanisms of Anesthesia, Humana Press, Totowa, NJ, 2002.

PUBLICATIONS

1. Antognini JF. Anaesthesia for Charcot-Marie-Tooth disease: a review of 86 cases. Canadian Journal of Anaesthesia 1992; 39(4):398-400.

2. Antognini JF and ND Kien. Cardiopulmonary bypass does not alter canine enflurane requirements. Anesthesiology 1992; 76:953-957.

3. Antognini JF. Intrathecal acetylsalicylic acid and indomethacin are not analgesic for a supramaximal stimulus. Anesthesia and Analgesia 1993; 76:1079-1082.

4. Antognini JF. Hypothermia eliminates isoflurane requirements at 20°C. Anesthesiology 1993; 78:1152-1156.

5. Antognini JF and GA Gronert. Succinylcholine causes profound hyperkalemia in hemorrhagic, acidotic rabbits. Anesthesia and Analgesia 1993; 77:585-588.

6. Melton AT, JF Antognini and GA Gronert. Prolonged duration of succinylcholine in patients receiving anticonvulsants: evidence for mild up-regulation of acetylcholine receptors? Canadian Journal of Anaesthesia 1993; 40(10):939-942.

7. Antognini JF and K Schwartz. Exaggerated anesthetic requirements in the preferentially anesthetized brain. Anesthesiology 1993; 79:1244-1249.

8. Antognini JF and PH Eisele. Anesthetic potency and cardiopulmonary effects of enflurane, halothane, and isoflurane in goats. Laboratory Animal Science 1993; 43(6):607-610.

9. Antognini JF. Splanchnic release of potassium after hemorrhage and succinylcholine in rabbits. Anesthesia and Analgesia 1994; 78:687-690.

10. Antognini JF, M Anderson, M Cronan, JP McGahan and GA Gronert. Ultrasonography: not useful in detecting susceptibility to malignant hyperthermia. Journal of Ultrasound in Medicine 1994; 13:371-374.

11. Antognini JF and ND Kien. A method for preferential delivery of volatile anesthetics to the *in situ* goat brain. Anesthesiology 1994; 80:1148-1154.

12. Antognini JF, BK Lewis and JA Reitan. Hypothermia minimally decreases nitrous oxide anesthetic requirements. Anesthesia and Analgesia 1994; 79:980-982.

13. Borges M and JF Antognini. Does the brain influence somatic responses to noxious stimuli during isoflurane anesthesia? Anesthesiology 1994; 81:1511-1515.

14. Antognini JF and ND Kien. Potency (minimum alveolar anesthetic concentration) of isoflurane is independent of peripheral anesthetic effects. Anesthesia and Analgesia 1995; 81:69-72.

15. Antognini JF and K Berg. Cardiovascular responses to noxious stimuli during isoflurane anesthesia are minimally affected by anesthetic action in the brain. Anesthesia and Analgesia 1995; 81:843-848.

16. Antognini JF. Creatine kinase alterations after acute malignant hyperthermia episodes and common surgical procedures. Anesthesia and Analgesia 1995; 81:1039-1042.

17. Gronert GA, NW Fleming and JF Antognini. Aberrant responses to muscle relaxants produced by diseases or drugs. Seminars in Anesthesia 1995; 14(4):283-290.

18. Hwang F, K Chun, JF Antognini and GA Gronert. Caffeine-halothane accuracy in MH testing. Acta Anaesthesiologica Scandinavica 1995; 39:1036-1040.

19. Antognini JF and K Mark. Hyperkalaemia associated with haemorrhagic shock in rabbits: modification by succinylcholine, vecuronium and blood transfusion. Acta Anaesthesiologica Scandinavica 1995; 39:1125-1127.

20. Antognini JF, R Wood and GA Gronert. Metocurine pharmacokinetics and pharmacodynamics in goats. Journal of Veterinary Pharmacology and Therapeutics 1995; 18:464-467.

21. Antognini JF. Movement associated with high cerebral concentrations of isoflurane: no evidence of seizure activity. Canadian Journal of Anaesthesia 1996; 43(3):310-314.

22. Antognini JF and GA Gronert. Extra-junctional receptors and neuromuscular blocking drugs. Current Opinion in Anaesthesiology 1996; 9:344-347.

23. Kien ND, JF Antognini, DA Reilly and PG Moore. Small-volume resuscitation using hypertonic saline improves organ perfusion in burned rats. Anesthesia and Analgesia 1996; 83:782-788.

24. Fleming NW, S Macres, JF Antognini and J Vengco. Neuromuscular blocking action of suxamethonium after antagonism of vecuronium by edrophonium, pyridostigmine or neostigmine. British Journal of Anaesthesia 1996; 77:492-495.

25. Antognini JF, PH Eisele and GA Gronert. Evaluation for malignant hyperthermia susceptibility in black-tailed deer. Journal of Wildlife Diseases 1996; 32(4): 678-681.

26. Antognini JF. The relationship among brain, spinal cord and anesthetic requirements. Medical Hypotheses 1997; 48:83-87.

27. Antognini JF and GA Gronert. Continued puzzles in malignant hyperthermia. Journal of Clinical Anesthesia 1997; 9:1-3.

28. Antognini JF and GA Gronert. Effect of temperature variation (22°C-44°C) on halothane and caffeine contracture testing in normal humans. Acta Anaesthesiologica Scandinavica 1997; 41: 639-642.

29. Antognini JF, MH Buonocore, EA Disbrow and E Carstens. Isoflurane anesthesia blunts cerebral responses to noxious and innocuous stimuli: a fMRI study. Life Sciences 1997; 61:PL349-354.

30. Antognini JF. Isoflurane potentiates metocurine via peripheral not central nervous system action. Journal of Veterinary Anaesthesia 1997; 24:6-9.

31. Disbrow E, M Buonocore, J Antognini, E Carstens and HA Rowley. The somatosensory cortex: a comparison of the response to noxious thermal, mechanical and electrical stimuli using functional magnetic resonance imaging. Human Brain Mapping 1998; 6:150-59.

32. Antognini JF, E Carstens, E Tabo and V Buzin. Effect of differential delivery of isoflurane to head and torso on lumbar dorsal horn activity. Anesthesiology 1998; 88:1055-61

33. Antognini JF, E. Carstens. A simple, quantifiable, and accurate method for applying a noxious mechanical stimulus. Anesthesia and Analgesia 1998; 87:1446-9.

34. Antognini JF, S. Jinks, V. Buzin, E. Carstens. A method for differential deilvery of intravenous drugs to the head and torso of the goat. Anesthesia and Analgesia 1998; 87:1450-2.

35. Antognini JF, E. Carstens. Macroscopic sites of anesthetic action: brain versus spinal cord. Toxicology Letters 1998; 100-101:51-58.

36 Antognini JF, E Carstens. Increasing isoflurane from 0.9 to 1.1 minimum alveolar concentration minimally affects dorsal horn cell responses to noxious stimulation. Anesthesiology 1999; 90:208-14.

37. Antognini JF, E Carstens, V Buzin. Isoflurane depresses motoneuron excitability by a direct spinal action: an F-wave study. Anesthesia and Analgesia 1999; 88:681-5.

38. Jinks S, JF Antognini, E Carstens V Buzin, C Simons. Isoflurane can indirectly depress lumbar dorsal horn activity via action within the brain. British Journal of Anaesthesia 1999; 82:244-49

39. Antognini JF, XW Wang. Isoflurane can indirectly depress auditory evoked potentials by action in the spinal cord. Canadian Journal of Anaesthesia 1999; 46:692-95

40. Melton AT, JF Antognini, GA Gronert. Caffeine- or halothane-induced contractures of masseter muscle are similar to those of vastus muscle in normal humans. Acta Anaesthesiologica Scandinavica 1999; 43:764-69

41. Antognini JF, XW Wang, E Carstens. Quantitative and qualitative effects of isoflurane on movement occurring after noxious stimulation. Anesthesiology 1999; 91:1064-71

42. Antognini JF, E Carstens. Isoflurane blunts electroencephalographic and thalamic/reticular formation responses to noxious stimulation in goats. Anesthesiology 1999; 91:1770-9

43. Antognini JF, XW Wang, E Carstens. Isoflurane action in the spinal cord blunts electroencephalographic and thalamic-reticular formation responses to noxious stimulation in goats. Anesthesiology 2000; 92:559-66

44. Antognini JF, XW Wang, M Piercy, E Carstens. Propofol directly

depresses lumbar dorsal horn neuronal responses to noxious stimulation. Canadian Journal of Anesthesia 2000; 47:273-79

45. Antognini JF, Saadi J, Wang XW, Carstens E, Piercy M. Propofol action in both spinal cord and brain blunts electroencephalographic responses to noxious stimulation in goats. Sleep 2000; 24:26-31

46. Antognini JF, XW Wang, E Carstens. Isoflurane anaesthetic depth in goats monitored using the bispectral index of the electroencephalogram. Veterinary Research Communications 2000; 24:361-370

47. Antognini JF, Sudo M, Sudo S, Carstens E. Isoflurane depresses electroencephalographic and medial thalamic responses to noxious stimulation via an indirect spinal action. Anesthesia and Analgesia 2000; 91:1282-8

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49. Antognini JF, Chen XG, Sudo M, Sudo S, Carstens E. Variable effects of nitrous oxide at multiple levels of the central nervous system in goats. Veterinary Research Communications 2001; 25:523-538

50. Rosenberg H, Antognini JF, Muldoon S. Testing for malignant hyperthermia. Anesthesiology 2002; 96:232-37

51. Antognini JF, Carstens E, Atherley R. Does the immobilizing effect of thiopental in brain exceed that of halothane? Anesthesiology 2002; 96:980-6

52. Jinks SL, Antognini JF, Martin JT, Jung S, Carstens E, Atherley R. Isoflurane, but not halothane, depresses c-fos expression in rat spinal cord at concentrations that suppress reflex movement after supramaximal noxious stimulation. Anesth Analg 2002; 95:1622-8

53. Martin JT, Tautz TJ, Antognini JF. Safety of regional anesthesia in Eisenmenger's syndrome.Reg Anesth Pain Med. 2002;27:509-13.

54. Antognini JF, Carstens E. In vivo characterization of clinical anaesthesia and its components.Br J Anaesth. 2002;89:156-66.

55. Jinks SL, Simons CT, Dessirier JM, Carstens MI, Antognini JF, Carstens E. C-fos induction in rat superficial dorsal horn following cutaneous application of noxious chemical or mechanical stimuli. Exp Brain Res. 2002;145:261-9.

56. Jinks SL, Martin JT, Carstens E, Jung SW, Antognini JF. Peri-mac depression of a nociceptive withdrawal reflex is accompanied by reduced dorsal horn activity with halothane but not isoflurane. Anesthesiology 2003; 98:1128-38

57. Antognini JF, Atherley RJ, Carstens E. Isoflurane action in spinal cord indirectly depresses cortical activity associated with electrical stimulation of the reticular formation. Anesthesia Analgesia 2003; 96:999-1003

58. Jinks SL, Antognini JF, Carstens E. Isoflurane depresses diffuse noxious inhibitory controls in rats between 0.8-1.2 MAC. Anesthesia Analgesia 2003; 97:111-116

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62. Jinks SL, Antognini JF, Carstens E. Spectral analysis of movement patterns during anesthesia.Anesth Analg. 2004; 98:698-702.

63. Jinks SJ, Antognini JF, Dutton RC, Carstens E, Eger EI. Isoflurane depresses windup of c-fiber evoked limb withdrawal with variable effects on nociceptive lumbar spinal neurons in rats. Anesth Analg 2004; 99:1413-9

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65. Jinks SJ, Antognini JF, Carstens E. Isoflurane differentially modulates medullary on and off neurons while suppressing hind-limb motor withdrawals. Anesthesiology 2004; 100:1224-34

66. Antognini JF, Jinks SJ, Carstens E, Atherley RJ. Preserved reticular neuronal activity during selective delivery of supra-clinical isoflurane concentrations to brain in goats and its association with spontaneous movement. Neuroscience Letters 2004; 361:94-7

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72. Cuellar JM, Dutton RC, Antognini JF, Carstens E. Differential effects of halothane and isoflurane on lumbar dorsal horn neuronal windup and excitability. Brit J Anaesth 2005; 94:617-25

73. Antognini JF, Carstens E. Anesthesia, Amnesia and the Amygdala: reducing the fear of intraoperative awareness. (Editorial) Anesthesiology 2005; 102:711-2

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77. Orth M, Barter L, Dominguez C, Atherley R, Carstens E, Antognini JF. Halothane and propofol differentially affect electroencephalographic responses to noxious stimulation. Brit J Anaesth 2005; 95:477-84

78. Jinks SL, Atherley RJ, Dominguez CL, Sigvardt KA, Antognini JF. Isoflurane disrupts central pattern generator activity and coordination in the lamprey isolated spinal cord. Anesthesiology 2005; 103:567-75.

79. Antognini JF, Jinks SL, Carstens EE. The spinal cord, anesthesia and immobility: a re-examination. International Congress Series 2005

80. Carstens E, Antognini JF. Anesthetic effects on the thalamus, reticular formation and related systems. Thalamus and Related Systems. 2005

81. Antognini JF, Barter L, Carstens E. Overview movement as an index of anesthetic depth in humans and experimental animals. Comp Med, 2005; 55(5): 413-8.

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